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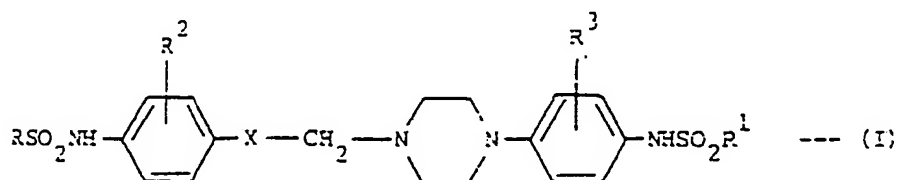
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(54) **Antiarrhythmic agents.**

(57) Antiarrhythmic agents of the formula:-



and their pharmaceutically acceptable salts,
 wherein R and R¹, which are the same or different, are C₁-C₄ alkyl, C₃-C₇ cycloalkyl, -CH₂CF₃, -CH₂Cl, -CF₃
 or -NH₂;
 R² and R³, which are the same or different, are H, halo, CF₃, C₁-C₄ alkyl or C₁-C₄ alkoxy;
 and X is -CH₂-, $\text{C} = \text{O}$ or -CH(OH)-.

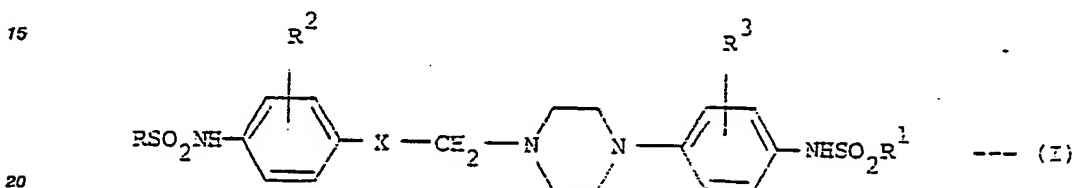
EP 0 257 864 A1

ANTIARRHYTHMIC AGENTS

This invention relates to certain sulfonamides which are antiarrhythmic agents.

The compounds of the invention prolong the duration of the action potential in cardiac muscle and conducting tissue, and thereby increase refractoriness to premature stimuli. Thus, they are Class III antiarrhythmic agents according to the classification of Vaughan Williams (Anti-Arrhythmic Action, E.M. Vaughan Williams, Academic Press, 1980). They are effective in atria, ventricles and conducting tissue both *in vitro* and *in vivo* and are therefore useful for the prevention and treatment of a wide variety of ventricular and supraventricular arrhythmias including atrial and ventricular fibrillation. Because they do not alter the speed at which impulses are conducted, they have less propensity than current drugs (mostly Class I) to precipitate or aggravate arrhythmias, and also produce less neurological side effects. Some of the compounds also have some positive inotropic activity and therefore are particularly beneficial in patients with impaired cardiac pump function.

Thus the invention provides compounds of the formula:-



and their pharmaceutically acceptable salts,

wherein R and R¹, which are the same or different, are C₁-C₄ alkyl, C₃-C₇ cycloalkyl, -CH₂CF₃, -CH₂Cl, -CF₃ or -NH₂; R² and R³, which are the same or different, are H, halo, CF₃, C₁-C₄ alkyl or C₁-C₄ alkoxy;

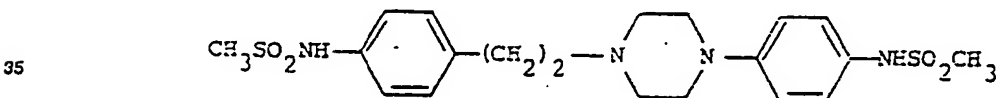
25 and X is -CH₂-, -C(=O)-

or -CH(OH)-.

"Halo" means F, Cl, Br or I. C₃ and C₄ alkyl and alkoxy groups can be straight or branched chain.

R and R¹ are each preferably C₁-C₄ alkyl. R and R¹ are most preferably CH₃. R² is preferably H and R³ is preferably H, CH₃, Cl or F. R² and R³ are most preferably H. X is preferably -CH₂-.

The preferred compound has the formula:-



The pharmaceutically acceptable salts of the compounds of the formula (I) include acid addition salts formed from acids which form non-toxic acid addition salts containing pharmaceutically acceptable anions, such as hydrochloride, hydrobromide, hydroiodide, sulphate or bisulphate, phosphate or hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, benzoate, methanesulphonate, besylate and p-toluenesulphonate salts. The compounds also form metal salts, examples of which are the alkaline earth and alkali metal salts, e.g. the sodium and potassium salts. The salts are preparable by conventional techniques.

For assessment of effects of the compounds on atrial refractoriness, guinea pig right hemiatra are mounted in a bath containing physiological salt solution, and one end is connected to a force transducer. Tissues are stimulated at 1 Hz using field electrodes. Effective refractory period (ERP) is measured by introducing premature stimuli (S₂) after every 8th basic stimulus (S₁). The S₁S₂ coupling interval is gradually increased until S₂ reproducibly elicits a propagated response. This is defined as ERP. The concentration of compound required to increase ERP by 25% (ED₂₅) is then determined. ERP is also measured in guinea pig right papillary muscles incubated in physiological salt solution. Muscles are stimulated at one end using bipolar electrodes and the propagated electrogram is recorded at the opposite end via a unipolar surface electrode. ERP is determined as above using the extrastimulus technique. Conduction time is obtained from a digital storage oscilloscope by measuring the interval between the stimulus artefact and the peak of the electrogram (i.e. the time required for the impulse to travel along the length of the muscle).

Atrial and ventricular ERP's are also measured in anaesthetised or conscious dogs by the extrastimulus technique whilst the atrium or right ventricle is being paced at a constant rate.

The compounds of the formula (I) can be administered alone but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. They can be administered both to patients suffering from arrhythmias and also prophylactically to those likely to develop arrhythmias. For example they may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. They may be injected parenterally, for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other solutes, for example, enough salts or glucose to make the solution isotonic.

For administration to man in the curative or prophylactic treatment of cardiac conditions such as ventricular and supraventricular arrhythmias, including atrial and ventricular fibrillation, it is expected that oral dosages of the compounds of the invention will be in the range from 1 to 75 mg daily, taken in up to 4 divided doses per day, for an average adult patient (70 kg). Dosages for intravenous administration would be expected to be within the range 0.5 to 10mg per single dose as required. A severe cardiac arrhythmia is preferably treated by the i.v. route in order to effect a rapid conversion to the normal rhythm. Thus for a typical adult patient individual tablets or capsules might for example contain 1 to 25mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier. Variations may occur depending on the weight and condition of the subject being treated as will be known to medical practitioners.

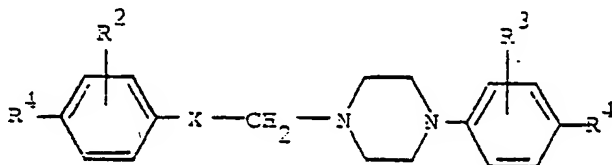
Thus the present invention provides a pharmaceutical composition comprising a compound of the formula (I) as defined above or pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

The invention also provides a method of preventing or reducing cardiac arrhythmias in a human being, which comprises administering to said human an effective amount of a compound of the formula (I) or pharmaceutically acceptable salt thereof, or of a pharmaceutical composition as defined above.

The invention yet further provides a compound of the formula (I) or a pharmaceutically acceptable salt thereof, for use as a medicament.

The invention also provides the use of a compound of the formula (I), or of a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the prevention or reduction of cardiac arrhythmias.

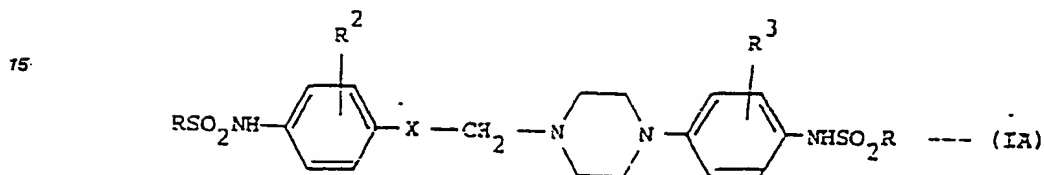
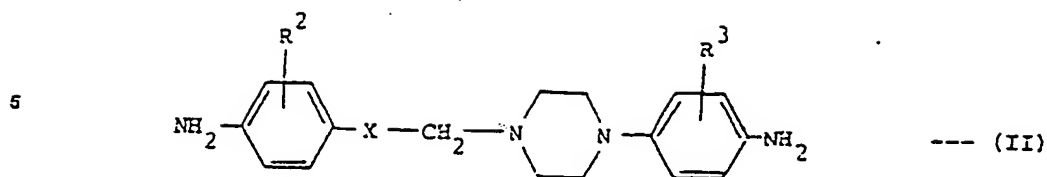
Also included within the scope of the invention are the intermediates of the formula:



where X, R² and R³ are as defined for formula (I) and each R⁴, which is the same, is -NO₂ or -NH₂. Most preferably, X is -CH₂- and R² and R³ are H.

The compounds of the formula (I) can be prepared by the following general routes:

(1) This route, which prepares compounds in which R and R¹ are the same, can be illustrated in general terms as follows:-

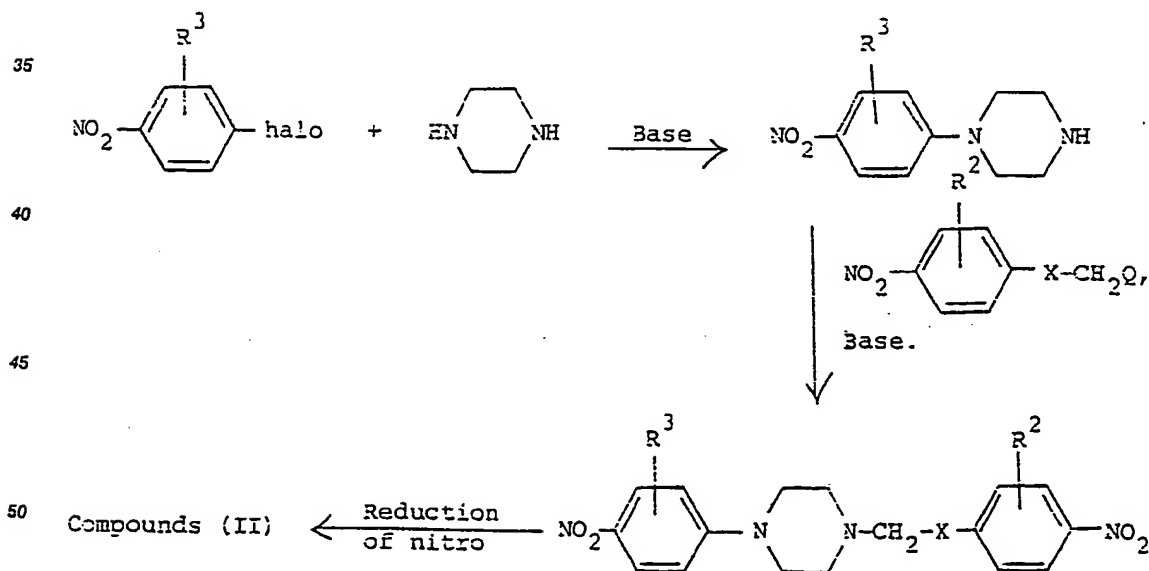


20 R, R², R³ and X are as defined for formula (I). To prepare compounds in which R is -NH₂, only sulphonyl chloride or bromide can be used in this reaction.

The reaction is typically carried out in a reaction-inert organic solvent, e.g. dichloromethane or dioxan, and preferably in the presence of a base, e.g. pyridine. Preferably, however, the reaction is carried out using pyridine as the solvent. Generally, the reaction proceeds satisfactorily at a temperature of from about 0° to 25°C, i.e. heating is not usually necessary. The reaction is typically carried out at room temperature. The product can be isolated and purified by conventional techniques.

When X is -CH(OH)-, it may be preferable to protect the hydroxy group by a conventional technique prior to acylation, followed by the removal of the protecting group.

30 The starting materials of the formula (II) are obtainable by conventional techniques as are known to those skilled in the art, and the following Examples illustrate typical syntheses of these compounds. Typical routes are illustrated in general terms as follows:-



55 In the above reaction scheme, Q is a leaving group such as halo, C₁-C₄ alkanesulphonyloxy, phenylsulphonyloxy or t-toluenesulphonyloxy. Q is preferably Br.

The first step in the reaction scheme leading to the compounds (II) is typically carried out in an excess of piperazine, typically about 3 times the weight of the halobenzene derivative, and with a small amount of co-solvent, e.g. dioxan, in an amount of, say, 1 ml. per gram. of said halobenzene derivative, and at the reflux temperature. The product is generally precipitated by diluting the cooled reaction mixture with water.

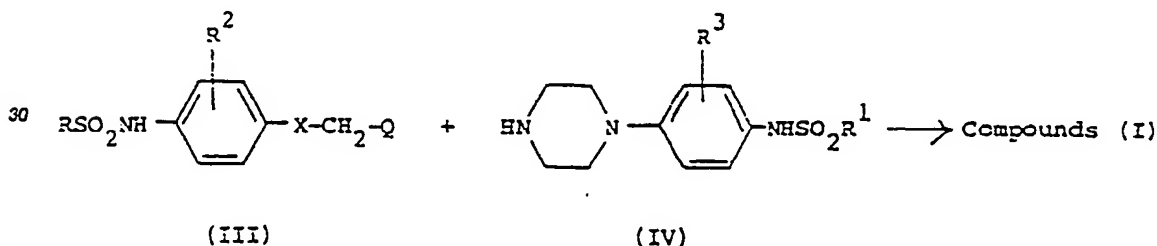
The second step is typically carried out under reflux in a reaction-inert organic solvent of b.p. 60-160°C, e.g. acetonitrile, ethanol or butanol, and preferably in the presence of a base such as sodium bicarbonate, potassium carbonate or triethylamine. Sodium iodide can also be added as a catalyst.

The final step can be carried out using conventional reducing agents, e.g. hydrogen in the presence of a palladium or nickel catalyst, tin and hydrochloric acid, stannous chloride or sodium dithionite. If X is a carbonyl group and reduction to -CH(OH)- is not desired, then a reducing agent which selectively reduces nitro should be chosen (e.g. sodium dithionite).

Alternatively, in the first stage of the above scheme it is sometimes preferable to use a mono-protected piperazine, typically 1-acetylpiperazine, in place of piperazine itself [see Examples 3(A) and 4(A).] In such circumstances, the reaction with the halobenzene derivative is typically carried out either using equimolar amounts of the halobenzene and 1-acetylpiperazine in the presence of a base, or using 1 mole of the halobenzene and 2 moles of 1-acetylpiperazine. The reaction is typically carried out in an organic solvent such as methanol or dimethylformamide at, say, from room temperature to 150°C. The protecting group is then removed by a conventional technique before the second stage. Acetyl groups are preferably removed by aqueous mineral acid or base, preferably hydrochloric acid at reflux.

(2) Compounds in which R and R¹ are both -NH₂ are however most conveniently prepared by a modification of route (1) by reacting the intermediate of the formula (II) with sulphamide, typically at 75° to 150°, and preferably under reflux, in a suitable solvent, e.g. dioxan.

(3) This route, which is capable of preparing compounds in which R and R¹ are the same or different, can be illustrated in general terms as follows:-



R, R¹, R², R³ and X are as defined for formula (I).

Q is a leaving group such as halo, C₁-C₄ alkanesulphonyloxy, benzenesulphonyloxy or p-toluenesulphonyloxy.

The preferred leaving groups are methylsulphonyloxy and bromo.

The reaction is typically carried out in an organic solvent such as methanol, ethanol or dichloromethane, at, say, from room temperature to 100°C. It is generally desirable to carry out the reaction in the presence of a base such as triethylamine. Indeed, an acid addition salt of (IV) (e.g. the hydrochloride) can be used as the starting material with excess base being present in the reaction mixture. The product (I) can be isolated and purified by conventional methods.

The starting materials of the formulae (III) and (IV), some of which are known compounds, are obtainable by conventional techniques as are illustrated in the following Examples. Typical techniques are illustrated in general terms as follows:-

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(a)

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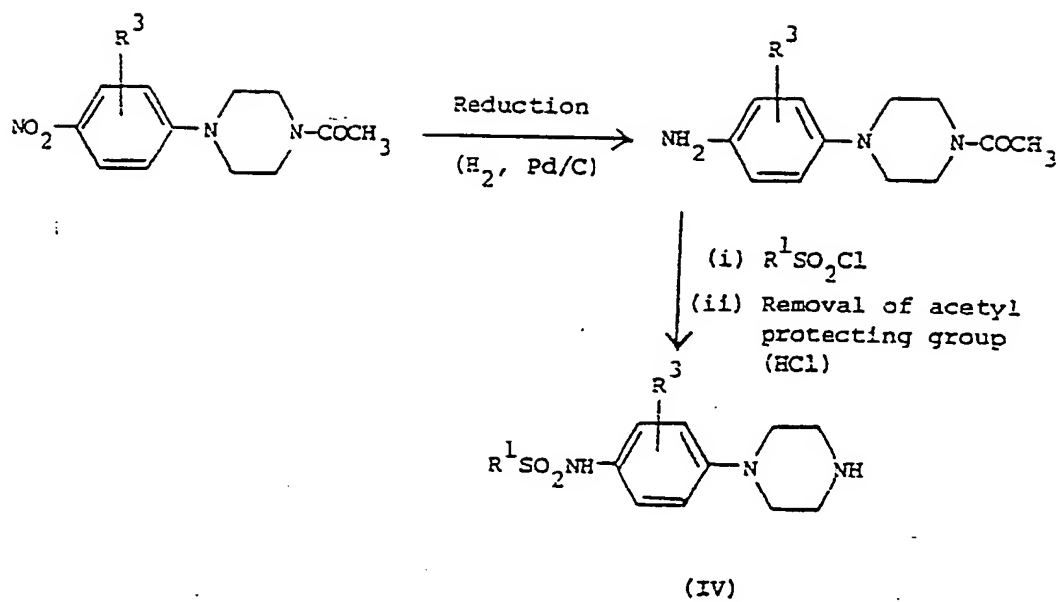
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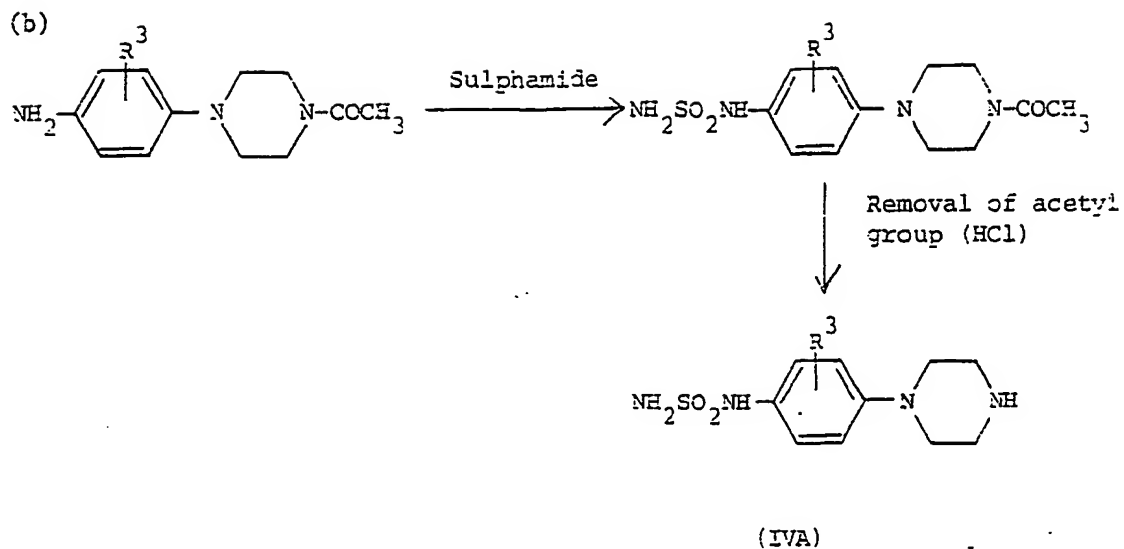
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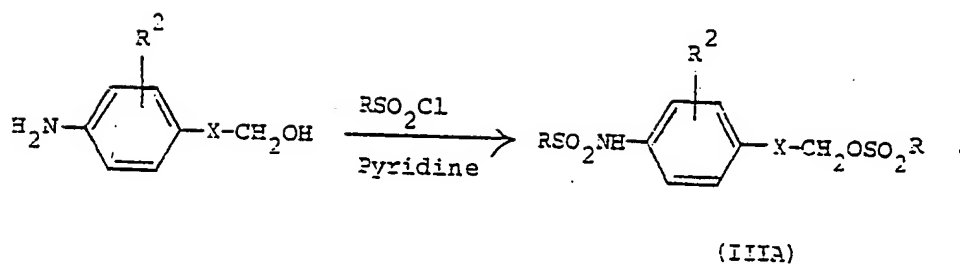
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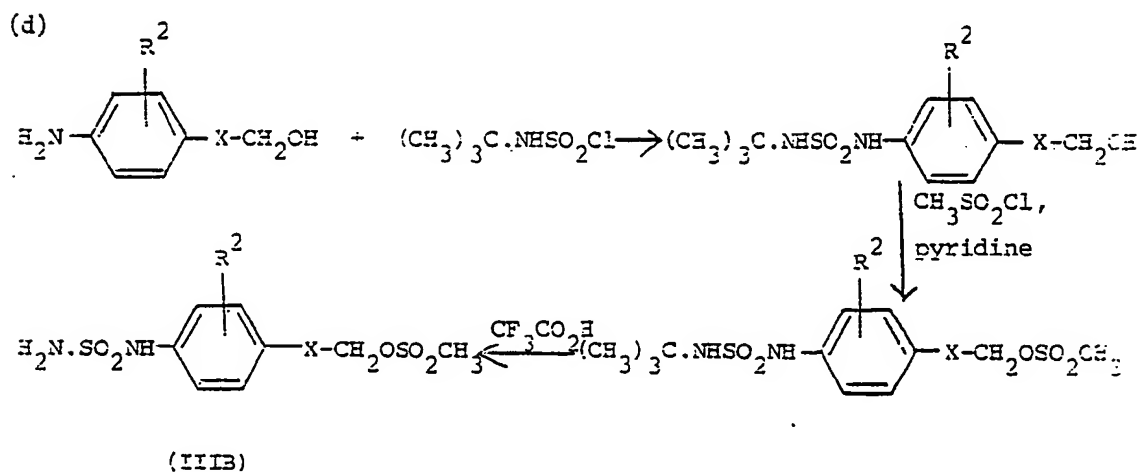




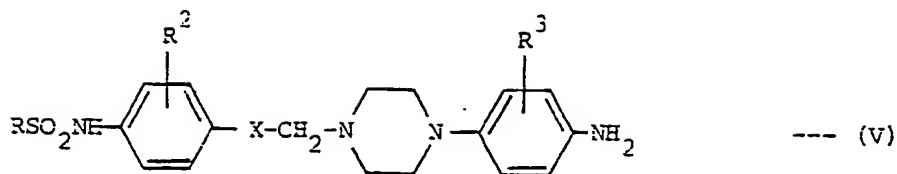
(c)



When R is $-\text{NH}_2$, the following route (d) is preferred.
and



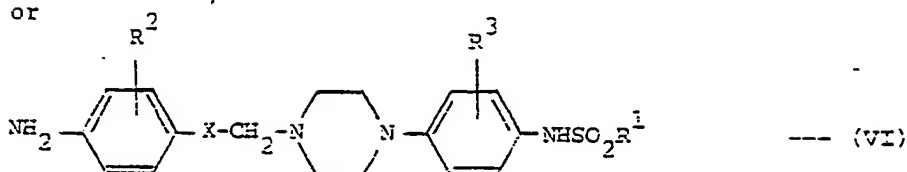
(4) The following general routes can also be used to prepare compounds in which R and R' are the same or different:-



10 R^1SO_2Y , $(R^1SO_2)_2O$ or sulphamide

15 Compound (I)

or

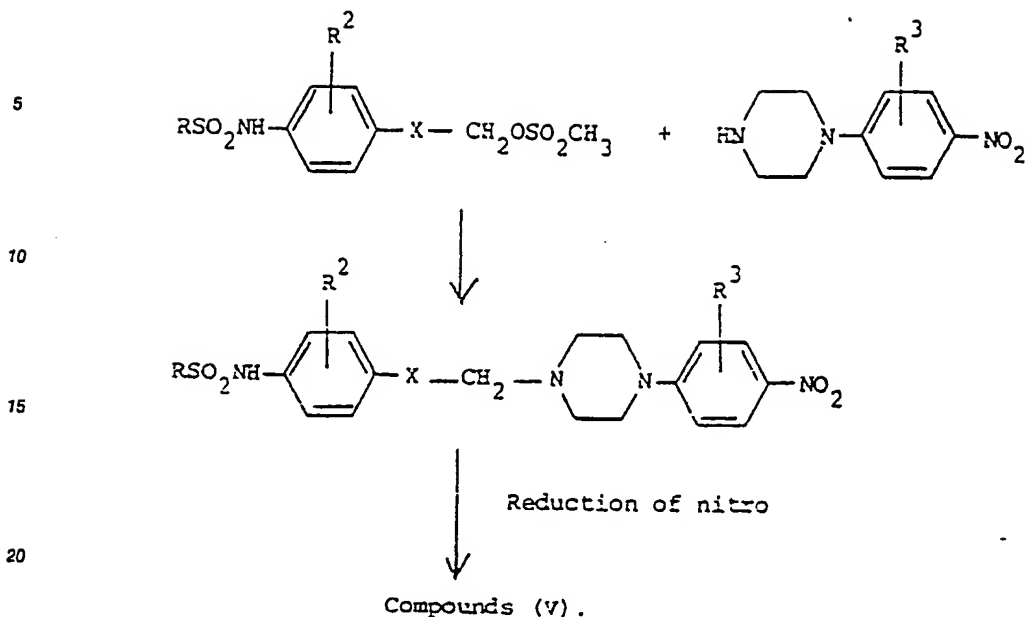


25 RSO_2Y , $(RSO_2)_2O$ or sulphamide

30 Compounds (I).

35 R, R¹, R², R³ and X are as defined for formula (I) except that in the sulphonic anhydride R and R¹ are not NH₂, and Y is as defined in route (1). The reactions with the sulphonyl or sulphamyl halide and the anhydride can be carried out in a similar manner to that described for route (1), and the reactions with sulphamide, as for route (2) above.

The starting materials (V) and (VI) are again available conventionally, e.g. as follows:-



An analogous sequence can be carried out to obtain the compounds (VI).

25 (5) Preparation of compounds in which X is -CH(OH)- is most conveniently carried out by the reduction of the corresponding carbonyl compounds (X = CO) in a conventional manner, e.g. using an anionic hydride derivative of boron or aluminium. The preferred reducing agent is sodium borohydride, the reaction typically being carried out in a reaction-inert organic solvent, e.g. ethanol or methanol optionally with dimethylformamide or water as co-solvent at temperatures of between room temperature and, say, 100°C. It is usually most convenient to carry out the reaction under reflux. The Compounds in which X is -CO- can also be reduced to compounds in which X is -CH₂- by the use of an appropriate reducing agent such as Zn/HCl.

The following Examples, in which all temperatures are in °C, illustrate the invention:-

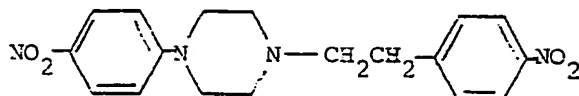
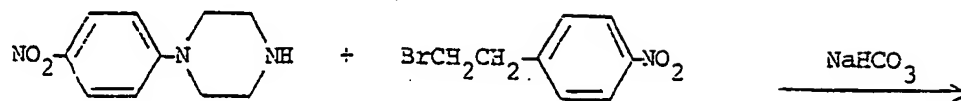
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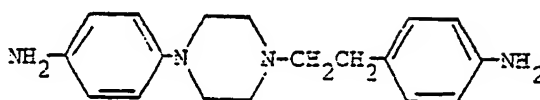
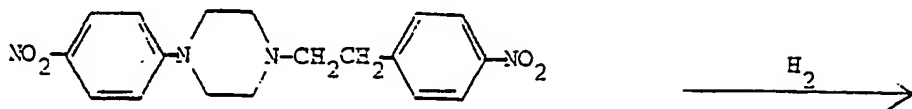
EXAMPLE 1(A) 1-(4-Nitrophenyl)-4-(4-nitrophenethyl)piperazine

1-(4-Nitrophenyl)piperazine (4.14 g), 4-nitrophenethyl bromide (4.6 g) and sodium bicarbonate (3.4 g) in acetonitrile (75 ml) were stirred under reflux for 1 day, and then evaporated to dryness. The residue was then triturated with water (300 ml), filtered, washed with water (300 ml), and the resulting solid was crystallized from ethyl acetate, yielding the title compound, (3.62 g), m.p. 143-5°.

N.M.R. (CDCl₃) δ = 2.4-2.8 (m, 6H); 2.96 (m, 2H); 3.46 (t, 4H); 6.84 (d, 2H); 7.40 (d, 2H); 8.16 (d, 2H); 8.18 (d, 2H) ppm.

30 Analysis %:-

Found: C,60.6; H,5.6; N,15.8;
Calculated for C₁₈H₂₀N₄O₄: C,60.7; H,5.7; N,15.7.

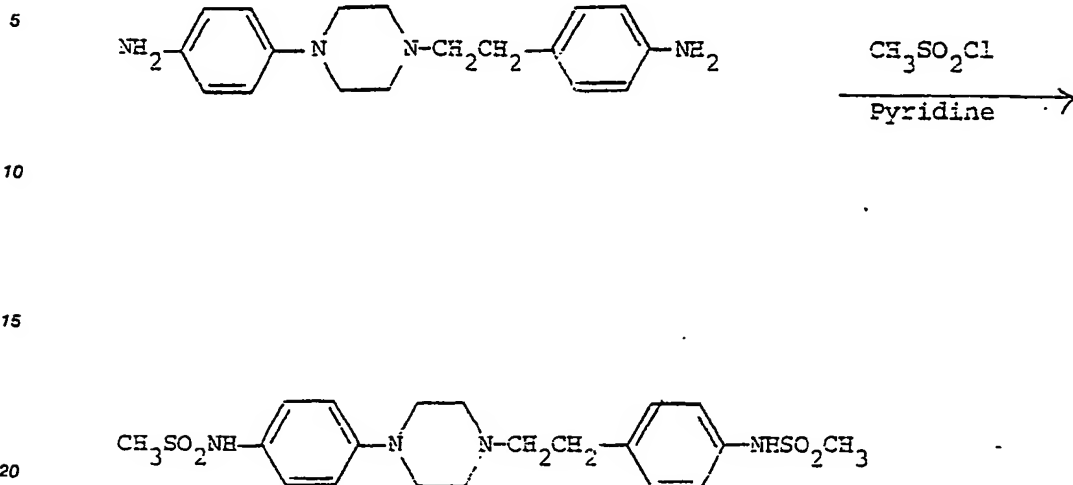
(B) 1-(4-Aminophenyl)-4-(4-aminophenethyl)piperazine

25 1-(4-Nitrophenyl)-4-(4-nitrophenethyl)piperazine (3.35 g) in methylated spirit (400 ml) was hydrogenated at 45° and 60 psi over 10% Pd/C (about 300 mg) for 3 hours. The catalyst was then removed by filtration and the filtrate evaporated to dryness, giving an off-white residual solid which was crystallized from ethyl acetate (charcoal); yield of the title compound 2.1 g, m.p. 156-8°.

N.M.R. (CDCl₃) δ = 2.55-2.8 (m, 8H); 3.10 (m, 4H); 3.3-3.65 (m, 4H); 6.6-6.7 (m, 4H); 6.85 (d, 2H); 7.02 (d, 2H) ppm.

Analysis %:-

Found: C, 72.9; H, 8.2; N, 18.9;
35 Calculated for C₁₈H₂₄N₄: C, 72.8; H, 8.3; N, 18.8.

(C) 1-(4-Methanesulphonamidophenyl)-4-(4-methanesulphonamidophenethyl)piperazine

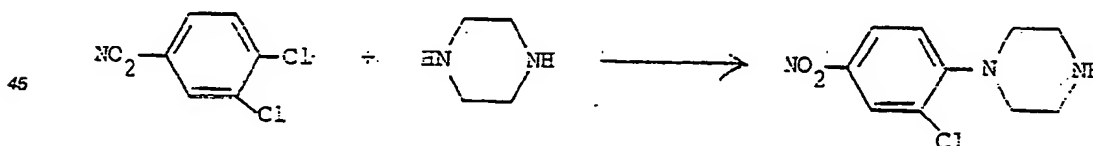
1-(4-Aminophenyl)-4-(4-aminophenethyl)piperazine (1.9 g) was dissolved in dry pyridine (15 ml) and methanesulphonyl chloride (1.85 g) was added dropwise with stirring. The mixture was stirred overnight, evaporated to dryness, and the residue triturated with aqueous sodium bicarbonate. The insoluble product was washed with water and digested with ethyl acetate/methanol then cooled and filtered, giving the pure title compound (2.1g) as a white solid, m.p. 254-6° (dec.).

N.M.R. (CD_3SOCD_3) δ = 2.33 (m, 6H); 2.70 (m, 2H); 2.84 (s, 3H); 2.94 (s, 3H); 6.88 (d, 2H); 7.08 (d, 2H); 7.11 (d, 2H); 7.19 (d, 2H); 9.40 (bs, 2H) ppm.

Analysis % :-

Found: C,52.9; H,6.2; N,12.3;

35 Calculated for $\text{C}_{20}\text{H}_{28}\text{N}_4\text{O}_4\text{S}_2$: C,53.1; H,6.2; N,12.4.

EXAMPLE 240 (A) 1-(2-Chloro-4-nitrophenyl)piperazine

3,4-Dichloronitrobenzene (10 g), piperazine (30 g) and dioxan (10 ml) were stirred for 4 hours under gentle reflux (internal temp. 120-130°). The mixture was then cooled and water (50 ml) was added; the desired product crystallized out and was filtered off, washed with water and dried; yield of the compound 11.32 g. A small portion (0.6 g) was recrystallized from petroleum b.p. 60-80°/ethyl acetate, yielding the product, (0.36 g), m.p. 100-102°.

N.M.R. (CDCl_3) δ = 2.9-3.3 (m, 8H); 6.98 (d, 1H); 7.91 (d $\frac{1}{2}$ H); 8.02-8.18 (m, $1\frac{1}{2}$ H) ppm.

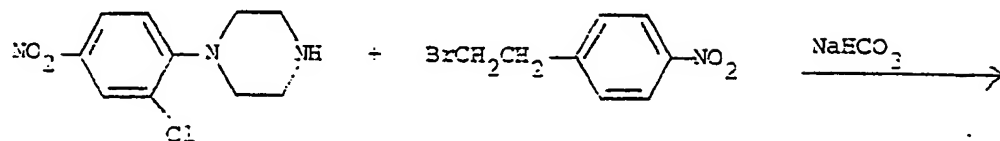
Analysis %:-

Found: C,49.6; H,5.0; N,17.2;
 Calculated for $C_{10}H_{12}ClN_3O_2$: C,49.7; H,5.0; N,17.4.

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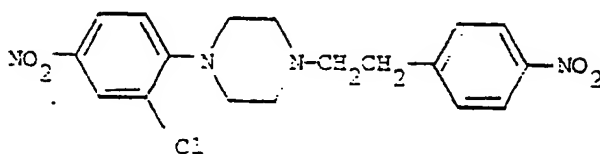
(B) 1-(2-Chloro-4-nitrophenyl)-4-(4-nitrophenethyl)piperazine

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The title compound, m.p. 102-4°, was prepared similarly to the procedure of Example 1(A) from 1-(2-chloro-4-nitrophenyl)piperazine (1.2 g), 4-nitrophenethyl bromide (1.15 g) and sodium bicarbonate (0.85 g). The yield of the title compound was 0.37 g (from ethyl acetate), m.p. 100-102°. A second batch had an m.p. of 102-4° (from ethyl acetate/methanol)

M.M.R. ($CDCl_3$) δ = 2.73 (m, 6H); 2.96 (m, 2H); 3.26 (m, 4H); 7.06 (d, 1H); 7.40 (d, 2H); 8.09-8.18 (m, 3H), 8.26 (d, 1H) ppm.

30

Analysis %:-

Found: C,55.4; H,4.8; N,14.4;
 Calculated for $C_{18}H_{19}ClN_4O_4$: C,55.3; H,4.9; N,14.3

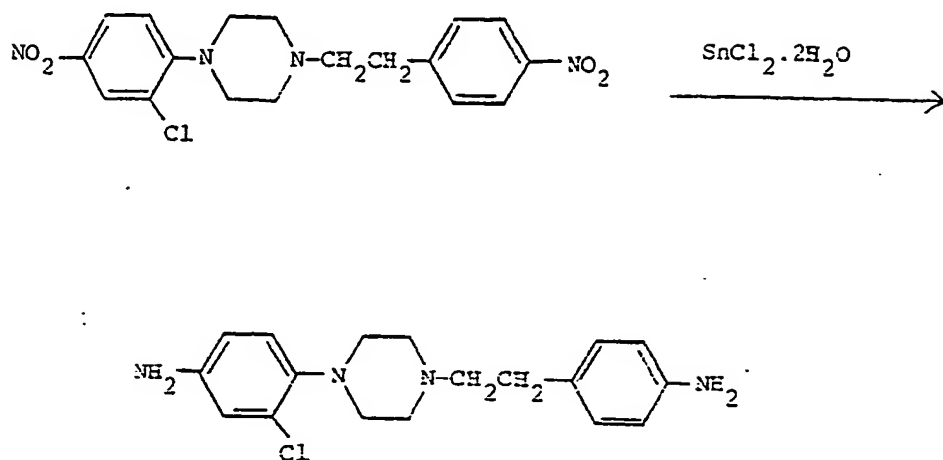
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(C) 1-(4-Amino-2-chlorophenyl)-4-(4-aminophenethyl)piperazine

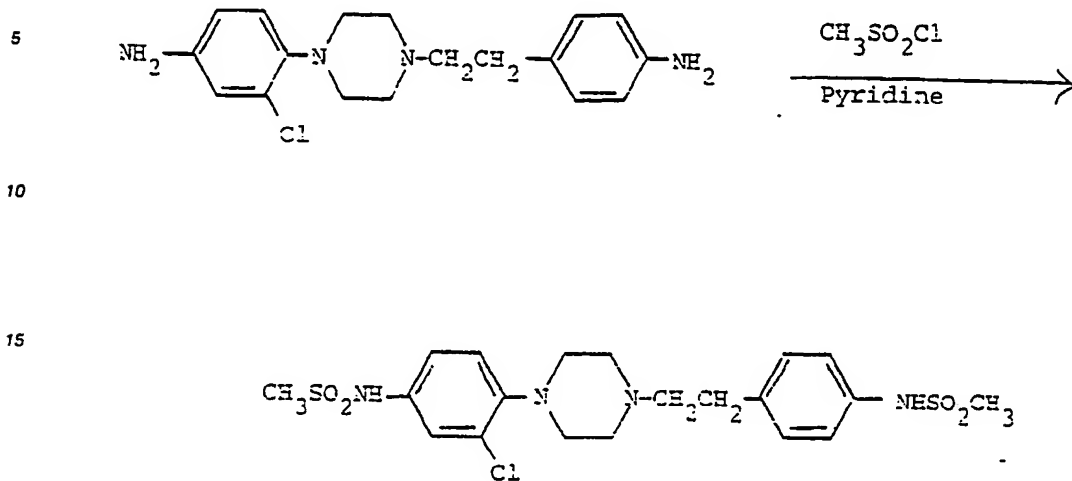
1-(2-Chloro-4-nitrophenyl)-4-(4-nitrophenethyl)piperazine (1.0 g), stannous chloride dihydrate (5.7 g) and ethanol (50 ml) were stirred under reflux for 1.25 hours, the mixture was evaporated to low bulk, and added to aqueous 5% sodium hydroxide (100 ml). The mixture was then extracted three times with dichloromethane and the combined organic extracts were dried (sodium sulphate) and evaporated to yield a yellow oil which solidified: yield of the title compound 0.6 g, m.p. 109-112°. It was used in the next stage without further purification.

N.M.R. (CDCl_3) δ = 2.6-2.8 (m, 8H); 3.03 (bs, 4H); 3.55 (s, 2H); 3.59 (s, 2H); 6.58 (m, 1H); 6.66 (d, 2H); 6.76 (d, 1H); 6.94 (d, 1H); 7.04 (d, 2H) ppm.

Analysis %:-

Found: C,64.6; H,7.0; N,16.6;

Calculated for $\text{C}_{18}\text{H}_{22}\text{ClN}_4$: C,65.3; H,7.0; N,16.9.

(D) 1-(2-Chloro-4-methanesulphonamidophenyl)-4-(4-methanesulphonamidophenethyl)piperazine

The title compound (0.52 g), was prepared similarly to the procedure of Example 1(C) from methanesulphonyl chloride (0.44 g), 1-(4-amino-2-chlorophenyl)-4-(4-aminophenethyl)piperazine (0.55 g), and pyridine (10 ml).

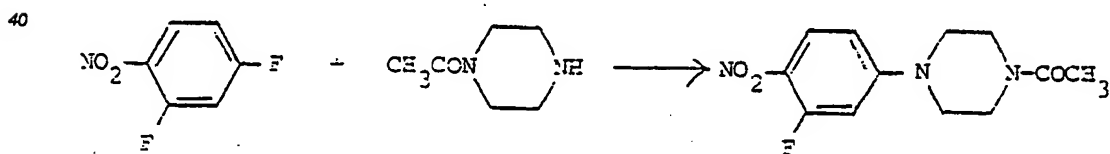
The m.p. of the product was 212-215° (from methanol/ethyl acetate).

N.M.R. (CD₃SOCD₃) δ = 2.55-2.58 (m, 4H); 2.72 (m, 2H); 2.94 (m, 8H); 3.33 (s, 4H); 7.10-7.23 (m, 7H); 9.63 (bs, 2H) ppm.

Analysis %:-

Found: C,49.4; H,5.6; N,11.1;

Calculated for C₂₀H₂₇ClN₄O₄S₂: C,49.3; H,5.6; N,11.5.

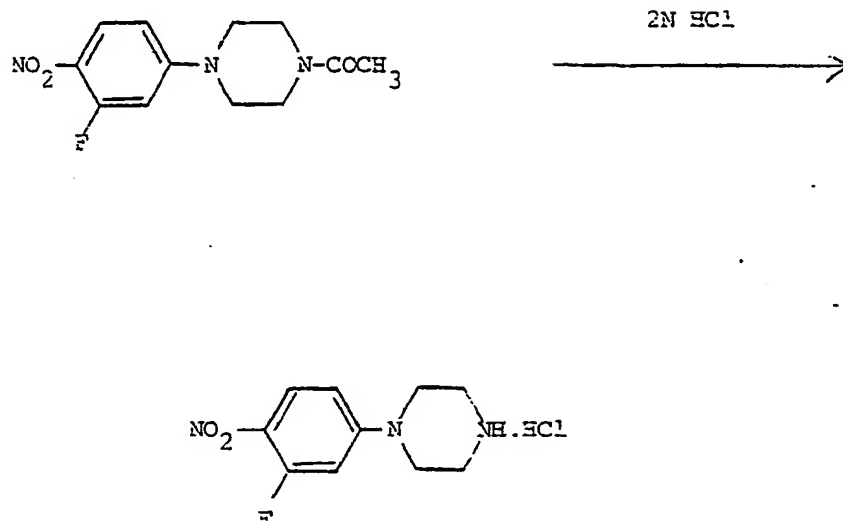
EXAMPLE 3(A) 1-Acetyl-4-(3-fluoro-4-nitrophenyl)piperazine

2,4-Difluoronitrobenzene (4.92 g) and 1-acetypiperazine (8.05 g) were dissolved in methanol (10 ml), kept overnight (17 hours) at ambient temperature, then diluted with methylene chloride (10 ml). The solution was washed with water (2 x 10 ml) and the methylene chloride layer was washed with water (2 x 40 ml) and evaporated to give a viscous orange oil (7.76 g) which slowly solidified. This product was dissolved in methanol (5 ml) and ether (15 ml) was added, precipitating a yellow solid (0.20 g) which was discarded. The filtrate was evaporated to yield a viscous oil (7.3 g) which was dissolved in 25 ml 20% methanol in ether, and chromatographed, under slight pressure, on Merck 60H (Trade Mark) t.l.c. grade silica, developing and eluting with the same solvent, collecting first the undesired isomer 1-acetyl-4-(5-fluoro-2-nitrophenyl)piperazine (4.73 g) from 120 to 250 ml eluate, identified by a lowest HF coupling of 5.8 Hz in the ¹⁹F N.M.R., consistent only with absence of hydrogen para to fluorine, followed by the desired 1-acetyl-4-(3-fluoro-4-nitrophenyl)piperazine (1.61 g), a yellow solid from 280 to 630 ml eluate, identified by a para HF coupling of -1.0 Hz in the ¹⁹F N.M.R.

N.M.R. (CDCl_3) δ = 2.18 (s, 3H); 3.48 (m, 4H); 3.69 (m, 2H); 3.82 (t, 2H); 6.53-6.64 (m, 2H); 8.08 (t, 1H) ppm.

The product was used directly in the next stage.

(B) 1-(3-Fluoro-4-nitrophenyl)piperazine hydrochloride

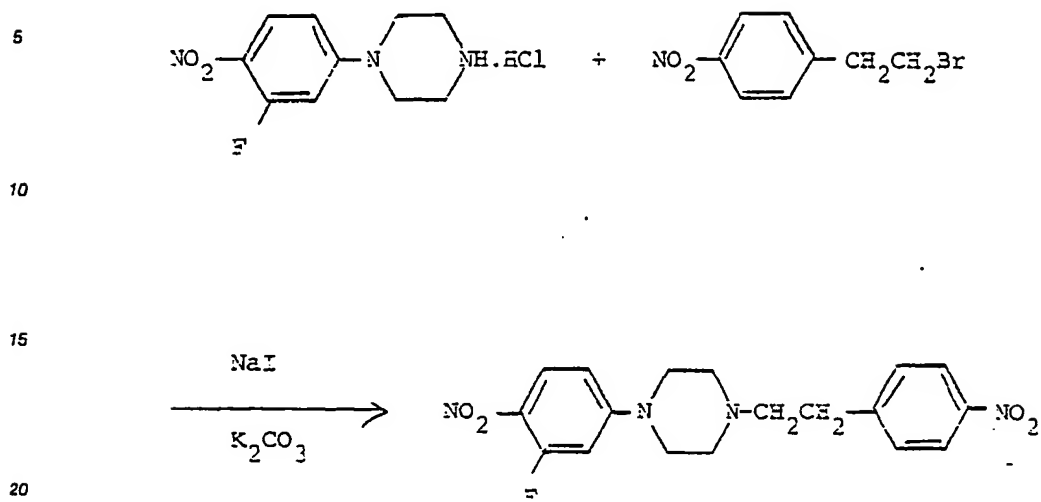


1-Acetyl-4-(3-fluoro-4-nitrophenyl)piperazine (1.08 g), and 2N hydrochloric acid (20 ml) were refluxed for 30 minutes. The solution was then evaporated to dryness, the residue triturated with methanol, the whole re-evaporated to remove hydrochloric acid, and the residue crystallized from methanol/ethanol, yielding the title compound, (0.78 g), m.p. 271-3°.

N.M.R. (CD_3SOCD_3) δ = 3.18 (t, 4H); 3.65 (t, 4H); 6.92 (d, 1H); 7.04 (d, 1H); 8.03 (dd, 1H); 9.68 (bs, 2H) ppm.

Analysis %:-

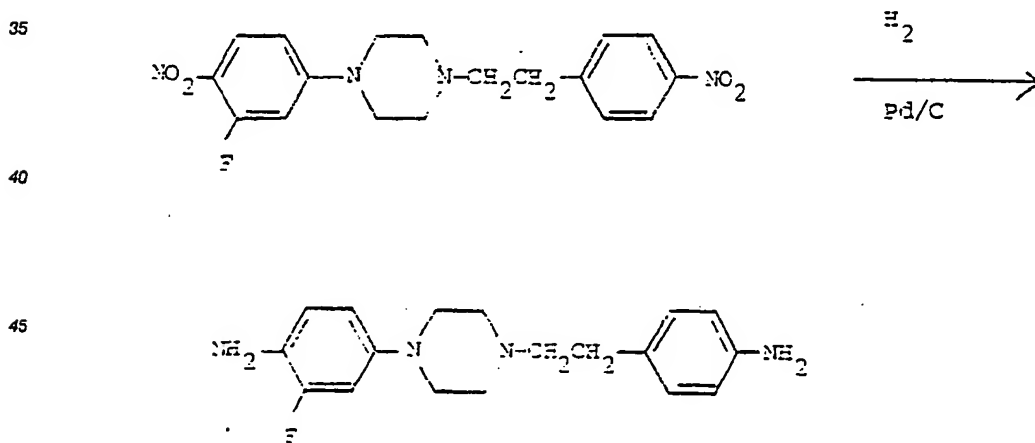
Found: C,45.9; H,4.9; N,16.2;
Calculated for $\text{C}_{10}\text{H}_{12}\text{FN}_3\text{O}_2\cdot\text{HCl}$: C,45.9; H,5.1; N,16.1.

(C) 1-(3-Fluoro-4-nitrophenyl)-4-(4-nitrophenethyl)piperazine

1-(3-Fluoro-4-nitrophenyl)piperazine hydrochloride (0.50 g), 4-nitrophenethyl bromide (0.44 g), sodium iodide (0.29 g) and potassium carbonate (0.27 g) in acetonitrile (11 ml) were refluxed for 2.75 hours. The mixture was then evaporated to dryness, partitioned between 5% methanol in dichloromethane and water, and the organic fraction chromatographed over silica, developing and eluting with 5% methanol in dichloromethane to yield the pure product as a yellow solid (0.19 g), R_f 0.57 (5% MeOH/CH₂Cl₂ on silica). The product was used directly in the next stage.

30

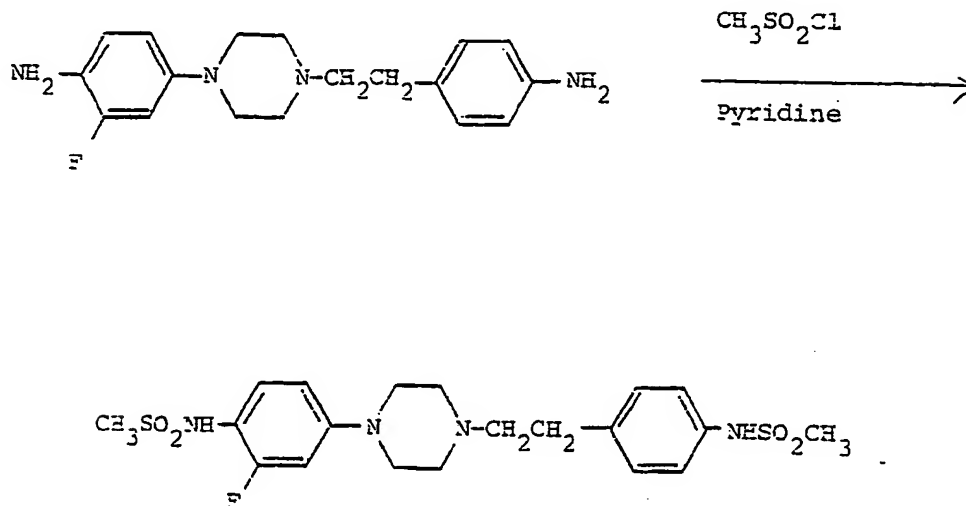
(D) 1-(3-Fluoro-4-aminophenyl)-4-(4-aminophenethyl)piperazine



1-(3-Fluoro-4-nitrophenyl)-4-(4-nitrophenethyl)piperazine (0.19 g) and 10% palladium on carbon (150 mg) were hydrogenated at 4 atmospheres and 60° until completion of hydrogen uptake. The catalyst was then filtered off, the solvent evaporated, and the residual product (0.06 g) used directly in the next stage.

55 N.M.R. (CDCl₃) δ = 2.55-2.82 (bm, 6H); 2.94-3.24 (bm, 6H); 3.63 (bs, 4H); 6.40-7.06 (complex, 7H) ppm.

(E) 1-(3-Fluoro-4-methanesulphonamidophenyl)-4-(4-methanesulphonamidophenethyl)piperazine



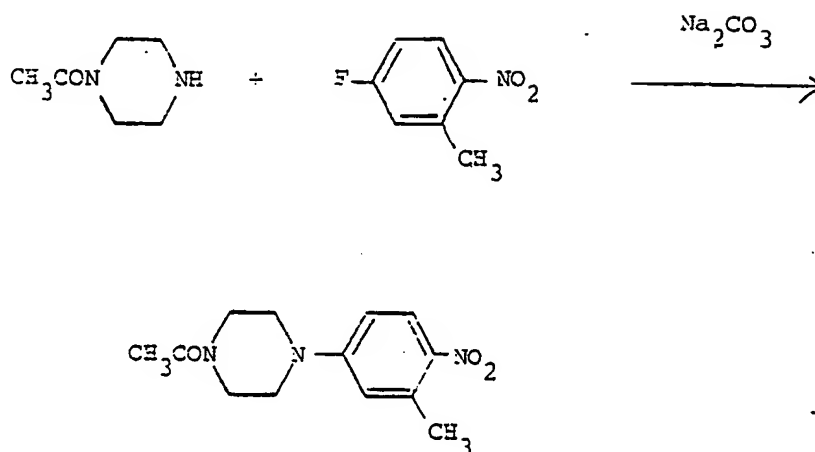
1-(3-Fluoro-4-aminophenyl)-4-(4-aminophenethyl)piperazine (0.06 g) was dissolved in pyridine (4.5 ml) and methanesulphonyl chloride (0.13 g) was added. The mixture was stirred at room temperature overnight, the pyridine removed by evaporation, and the residue chromatographed over silica, developing and eluting with 10% methanol in dichloromethane. The fractions containing the product were evaporated to give a residue (0.030 g) which was crystallized from methanol, yielding the pure title compound, (0.016 g), m.p. 232-4°.

N.M.R. (CDCl₃): δ = 2.54 (m, 6H); 2.72 (m, 2H); 2.89 (s, 3H); 2.94 (s, 3H); 3.14 (m, 4H); 6.70-6.85 (m, 2H); 7.08 + 7.12 (3H); 7.18 + 7.22 (2H); 9.35 (vbs, 2H) ppm.

Analysis %:-

35 Found: C, 51.1; H, 5.9; N, 11.9

Calculated for C₂₂H₂₇FN₄O₄S₂: C, 51.0; H, 5.8; N, 11.9.

EXAMPLE 4(A) 1-Acetyl-4-(3-methyl-4-nitrophenyl)piperazine

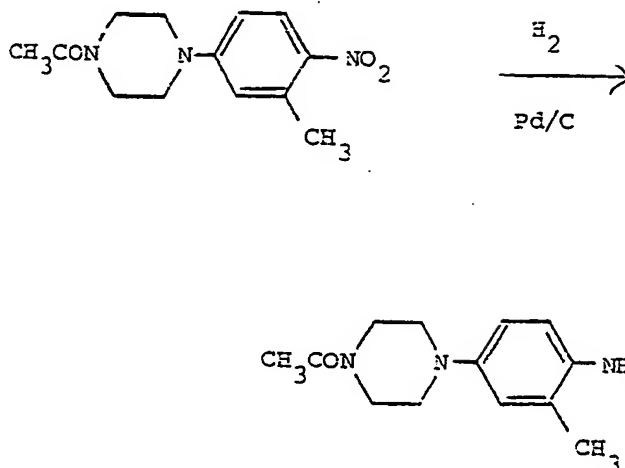
1-Acetylpiperazine (6.23 g), 5-fluoro-2-nitrotoluene (7.51 g) and sodium carbonate (5.12 g) in dimethylformamide (40 ml) were stirred at 100° overnight, evaporated, and the residue partitioned between ethyl acetate and water. The organic layer was dried (sodium sulphate), evaporated, and the residue chromatographed over Merck (Trade Mark) t.l.c. grade silica, developing and eluting with 5% methanol in dichloromethane, yield 10.92 g of the title compound. A small portion was recrystallized from methanol/ethyl acetate, m.p. $133-7^\circ$.

N.M.R. (CDCl_3) δ = 2.18 (s, 3H); 2.64 (s, 3H); 3.43 (m, 4H); 3.66 (m, 2H); 3.81 (m, 2H); 6.69 (m, 2H), 8.11 (d, 1H) ppm.

Analysis %:-

Found: C, 58.9; H, 6.6; N, 16.2;

Calculated for $\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_3$: C, 59.3; H, 6.5; N, 16.0.

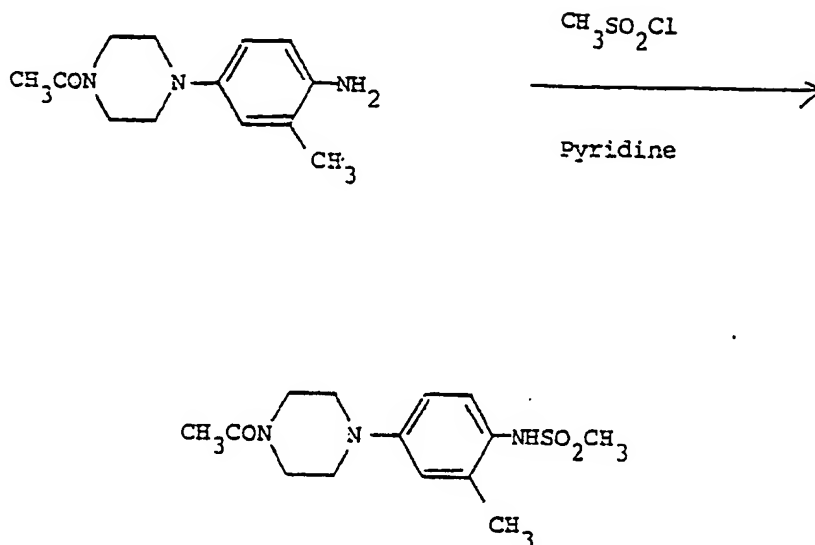
(B) 1-Acetyl-4-(4-amino-3-methylphenyl)piperazine

1-Acetyl-4-(3-methyl-4-nitrophenyl)piperazine (0.5 g) and 5% palladium on carbon (0.1 g) in ethanol (20 ml) were hydrogenated at 60° and 60 p.s.i. for 2 hours after which the catalyst was filtered off and the filtrate evaporated. The residue was partitioned between dichloromethane and water, and the aqueous layer extracted two more times with dichloromethane. The combined organic layers yielded 0.42 g of residue (of the title compound) on evaporation. This was recrystallized, m.p. 126-9° (methanol/ethyl acetate).

N.M.R. (CDCl₃) δ = 2.14 (s, 3H); 2.17 (s, 3H); 3.01 (m, 4H), 3.43 (bs, 2H); 4.60 (m, 2H); 4.87 (m, 2H).

Analysis % :-

Found: C,66.7; H,8.2; N,17.9;
Calculated for C₁₃H₁₉N₃O: C,66.9; H,8.2; N,18.0.

(C) 1-Acetyl-4-(4-methanesulphonamido-3-methylphenyl)piperazine

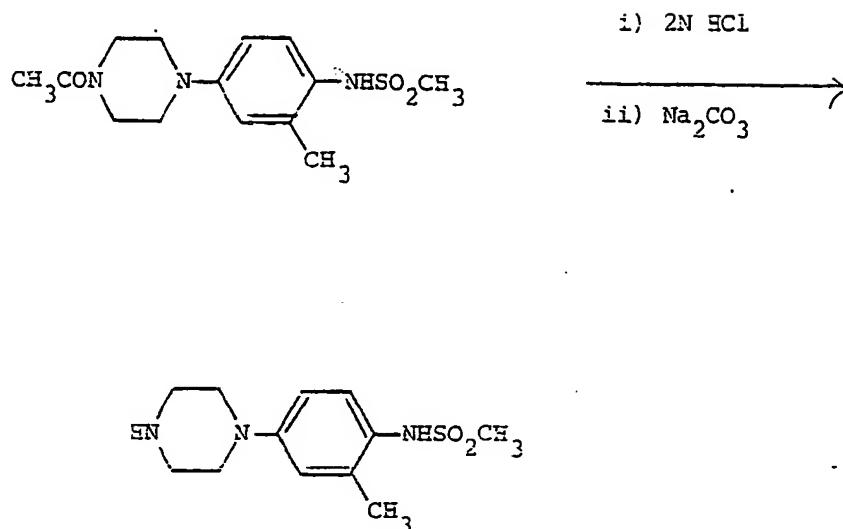
1-Acetyl-4-(4-amino-3-methylphenyl)piperazine (7.89 g) was dissolved in pyridine (130 ml). Methanesulphonyl chloride (7.9 ml) was added dropwise with stirring. The mixture was reduced in volume after 2 hours by evaporation and then stirred overnight. The resulting slurry was partitioned between water (125 ml) and dichloromethane (100 ml), and the aqueous layer was further extracted with dichloromethane (2 x 100 ml), 5% methanol in dichloromethane (2 x 100 ml), and ethyl acetate (2 x 125 ml). The combined organic layers were dried (sodium sulphate) and evaporated, and the residue was chromatographed in 5% methanol in dichloromethane over t.l.c. grade silica, the product-containing fractions, after evaporation, yielding a foam (5.93 g), Rf 0.29 (5% methanol/ dichloromethane/silica), used directly in step (D). A small sample from a second run was recrystallized from ethyl acetate/hexane, m.p. 153-4°.

N.M.R. (CDCl₃) δ = 2.14 (s, 3H); 2.34 (s, 3H); 2.97 (s, 3H); 3.17 (m, 4H); 3.61 (t, 2H); 3.76 (t, 2H); 6.12 (s, 1H); 6.76 (m, 2H); 7.28 (m, 1H) ppm.

Analysis %:-

Found : C,54.0; H,6.8; N,13.4;

40 Calculated for C₁₄H₂₁N₃O₃S: C,54.0; H,6.8; N,13.5.

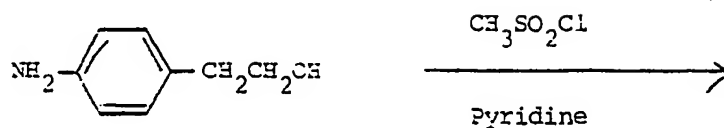
(D) 1-(4-Methanesulphonamido-3-methylphenyl)piperazine 1/4 hydrate

25 1-Acetyl-4-(4-methanesulphonamido-3-methylphenyl)piperazine (5.93 g) and 2N aqueous hydrochloric acid (85 ml) were refluxed for 2 hours, cooled, evaporated to low bulk, basified with sodium carbonate to pH 9-10 and extracted with 5 x 100 ml 5% methanol in dichloromethane. The organic layers were combined and evaporated to give the title compound as a brown foam, (4.78 g), m.p. 79-81°.

N.M.R. (CDCl_3) δ = 2.13 (s, 3H); 2.96 (s, 3H); 3.05 (m, 4H); 3.15 (m, 4H); 6.76 (m, 2H); 7.16 (m, 1H).

Analysis %:-

Found: C, 52.6; H, 6.8; N, 15.2;
 Calculated for $\text{C}_{12}\text{H}_{19}\text{N}_3\text{O}_2\text{S} \cdot 1/4 \text{H}_2\text{O}$: C, 52.6; H, 7.2; N, 15.3.

(E) 4-Methanesulphonamidophenethyl methanesulphonate

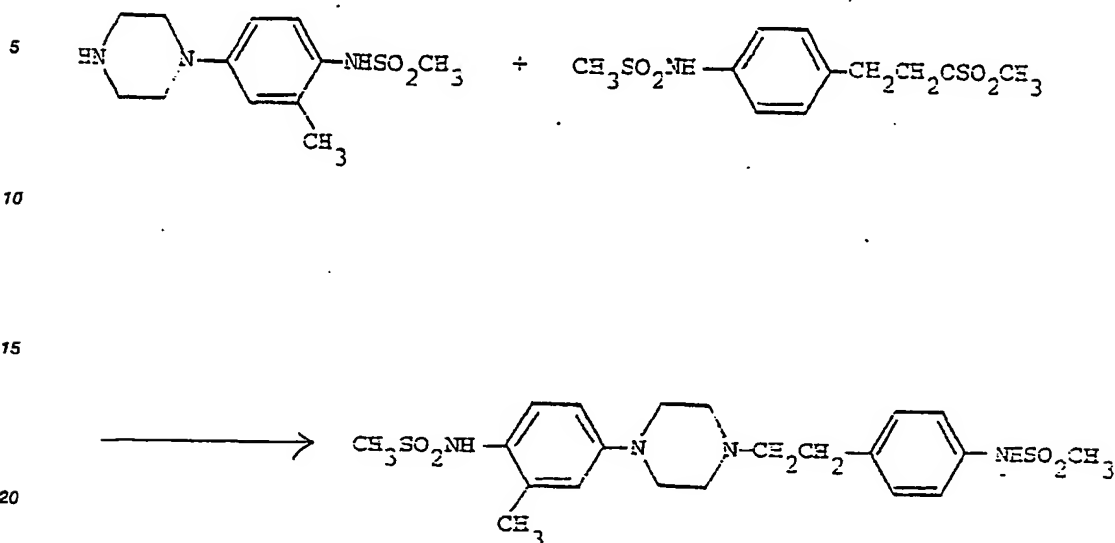
4-Aminophenethyl alcohol (2.74 g) was dissolved in dichloromethane (10 ml) and pyridine (5 ml) and then methanesulphonyl chloride (2 x 2.52 g) was added in 2 portions one hour apart, with stirring at 0°. After a further 2 hours, the mixture was acidified (to pH about 2) with 2N aqueous hydrochloric acid. The title compound (4.85 g) was filtered from the two-phase mixture. The organic layer plus a further dichloromethane extract of the aqueous layer yielded a further 0.95 g product after drying (sodium sulphate) and evaporation. The combined solids were washed with ether and recrystallized from ethyl acetate, yield of the title compound 4.13 g, m.p. 135-7°.

N.M.R. [(CD₃)₂CO] δ = 3.07 (s, 3H); 3.10 (s, 3H); 3.15 (t, 2H); 4.52 (t, 2H); 7.36 (s, 4H); 8.47 (bs, 1H) ppm.

Analysis %:-

Found: C,40.6; H,5.2; N,4.9;
Calculated for C₁₀H₁₅NO₅S₂: C,40.9; H,5.2; N,4.8.

(F) 1-(4-Methanesulphonamido-3-methylphenyl)-4-(4-methanesulphonamidophenethyl)piperazine



4-Methanesulphonamidophenethyl methanesulphonate (1.47 g) and 1-(4-methanesulphonamido-3-methylphenyl)piperazine 1/4 hydrate (1.37 g) in ethanol (15 ml) were refluxed overnight, evaporated to dryness, and partitioned between ethyl acetate and water. The title compound (0.2g) was filtered from the 2-phase mixture and recrystallised from methanol/acetone, yield 0.128 g, m.p. 235-7°.

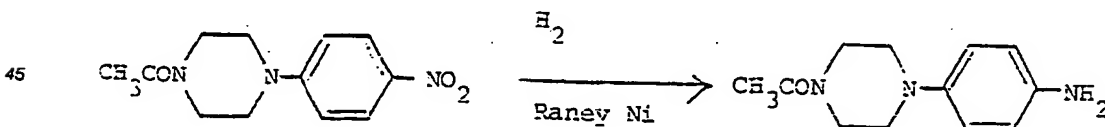
N.M.R. (CD₃SOCD₃) δ = 2.23 (s, 3H); 2.54 (m, 6H); 2.72 (t, 2H); 2.87 (s, 3H); 2.94 (s, 3H); 3.11 (m, 4H); 6.70-6.84 (m, 2H); 7.03-7.12 (s, 3H), 7.13-7.21 (d, 2H), 9.13 (bs, 2H) ppm.

Analysis %:-

Found: C,54.3; H,6.4; N,12.0;
 35 Calculated for C₂₁H₃₀N₄O₄S₂: C,54.0; H,6.5; N,12.0.

EXAMPLE 5

40 (A) 1-Acetyl-4-(4-aminophenyl)piperazine



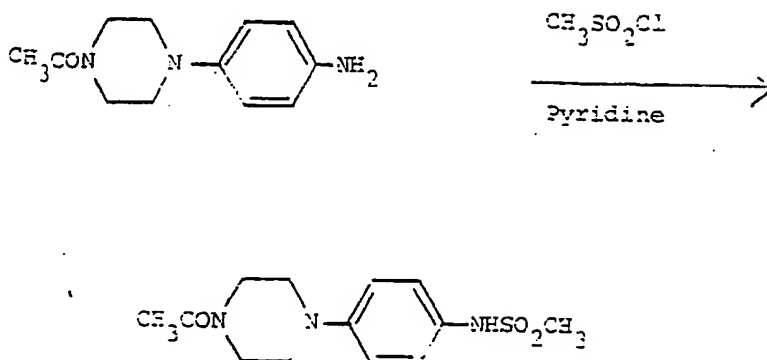
1-Acetyl-4-(4-nitrophenyl)piperazine [Ger. Pat. 1,239,940; Chem. Abs., 67, 101031z (1967)] (76.64 g) in ethanol (1000 ml) was hydrogenated over Raney nickel at 40° and 60 p.s.i. for 4 hours. The catalyst was then filtered off and the filtrate evaporated to give a residual solid which was crystallised from ethyl acetate, yield of the title compound 47.88 g, m.p. 129-130°.

N.M.R. (CDCl₃) δ = 2.12 (s, 3H); 2.90-3.09 (t, 4H); 3.50-3.8 (m, 4H); 6.52, 6.67, 6.88 (ABq, 4H) ppm.

55

Analysis %:-

Found: C,65.8; H,7.8; N,19.5;
 Calculated for $C_{12}H_{17}N_3O$: C,65.7; H,7.8; N,19.2.

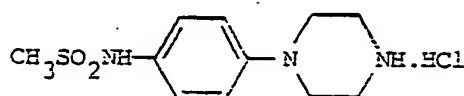
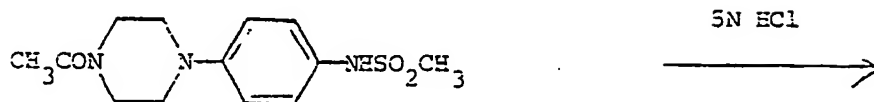
(B) 1-Acetyl-4-(4-methanesulphonamidophenyl)piperazine

To 1-Acetyl-4-(4-aminophenyl)piperazine (10.96 g) in ice-cold pyridine (100 ml) was added methanesulphonyl chloride (6.3 g) dropwise. The mixture was then stirred at ambient temperature overnight and the pyridine removed in vacuo. The residue was triturated with aqueous sodium bicarbonate, and the resulting solid was washed (water) and crystallized from methanol/ethyl acetate (charcoal). The yield of the title compound was 9.97 g, m.p. 165-7°.

N.M.R. (CDCl_3) δ = 2.17 (s, 3H); 2.97 (s, 3H); 3.16 (m, 4H); 3.63 (t, 2H); 3.77 (t, 3H); 6.67 (s, 1H); 6.91 (d, 2H); 7.20 (d, 2H) ppm.

Analysis %:-

Found: C,52.4; H,6.3; N,14.1;
 Calculated for $C_{13}H_{19}N_3O_3S$: C,52.5; H,6.4; N,14.1.

C) 1-(4-Methanesulphonamidophenyl)piperazine hydrochloride

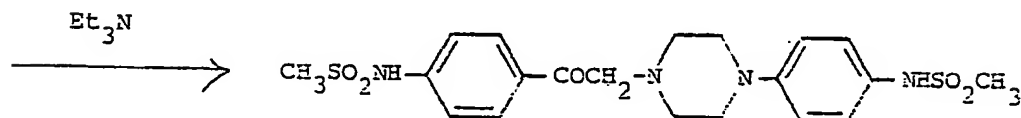
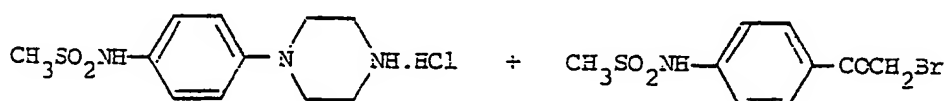
20 1-Acetyl-4-(4-methanesulphonamidophenyl)piperazine (9.6 g) and 5N aqueous hydrochloric acid (100 ml) were heated at 100° for 1 hour, the solvent was evaporated, and the residue dried by azeotrope with toluene. The residue was crystallised from ethanol, yield of the title compound 8.26 g, m.p. 230° (dec.).

25 N.M.R.(CD₃SOCD₃) δ = 2.85 (s, 3H); 3.15 (s, 4H); 3.30 (m, 4H); 6.95 (d, 2H); 7.10 (d, 2H); 9.27 (bs, 2H); 9.37 (s, 1H) ppm.

Analysis %:-

Found: C,44.5; H,6.3; N,14.0;

30 Calculated for C₁₁H₁₇N₃O₂S.HCl C,45.3; H,6.2; N,14.4.

(D) 1-(4-Methanesulphonamidophenyl)-4-(4-methanesulphonamidophenacyl)piperazine

55 1-(4-Methanesulphonamidophenyl)piperazine hydrochloride (1.18 g), 4-methanesulphonamidophenacyl bromide (1.16 g), [see. J. Med. Chem., 9, 88 (1966)], triethylamine (0.82 g), methanol (10 ml) and dichloromethane (10 ml) were warmed briefly to attain homogeneity, then stirred at ambient temperature for 4 hours, evaporated to dryness, the residue triturated and washed with water, and then crystallized from methanol/acetone. The yield of the title compound was 0.88 g, m.p. 222-5° (dec.).

N.M.R. (CD_3SOCD_3) δ = 2.62 (bs, 4H); 3.10 (bs, 8H); 3.34 [s, 2H (+ H_2O)]; 3.82 (s, 2H); 6.88 (d, 2H); 7.07 (d, 2H); 7.27 (d, 2H); 7.98 (d, 2H); 9.22 (s, 1H); 10.31 (bs, 1H) ppm.

5 Analysis %:-

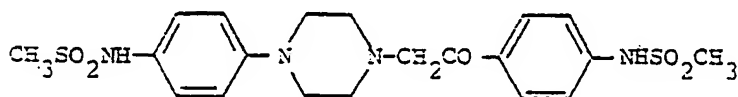
Found: C,51.2; H,5.2; N,11.7;
Calculated for $\text{C}_{20}\text{H}_{22}\text{N}_4\text{O}_5\text{S}_2$: C,51.5; H,5.6; N,12.0.

10

EXAMPLE 6

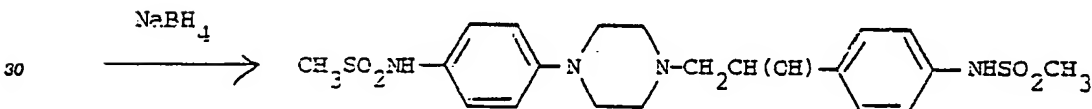
1-(4-Methanesulphonamidophenyl)-4-[2-hydroxy-2-(4-methanesulphonamidophenyl)ethyl]piperazine

15



20

25



35 1-(4-Methanesulphonamidophenyl)-4-(4-methanesulphonamidophenyl)piperazine [see Example 5(D)] (0.77 g) was dissolved in ethanol (3 ml) and dimethylformamide (5 ml). Sodium borohydride (0.125 g) was then added portionwise over 5 minutes, and the mixture was stirred for 2½ hours at ambient temperature. A further 25 mg. sodium borohydride was then added and the reaction mixture was heated at 60° for 2 hours. A further 20 mg. of borohydride was added, and the reaction mixture was heated at 70° for 4½ hours. The mixture was then diluted with water, precipitating the impure product containing some unreduced starting material (0.51 g after drying). This impure product was refluxed for 4½ hours in ethanol (35 ml), adding sodium borohydride (110 mg) portionwise during the first 2 hours. The mixture was then evaporated, the residue washed with water, and crystallized from methanol, yield of the pure title compound 0.118 g., m.p. 230-2° (dec.).

45 N.M.R. (CD_3SOCD_3) δ = 2.37-2.56 (m, 2H); 2.62 (m, 4H); 2.85 (s, 3H); 2.94 (s, 3H); 4.72 (m, 1H); 5.02 (d, 1H); 6.90 (d, 2H); 7.06 (d, 2H); 7.14 (d, 2H); 7.32 (d, 2H); 9.1-9.8 (bs, 2H) ppm.

Analysis %:-

50 Found: C,50.9; H,6.1; N,11.9;
Calculated for $\text{C}_{20}\text{H}_{22}\text{N}_4\text{O}_5\text{S}_2$: C,51.3; H,6.0; N,12.0.

55

EXAMPLE 7**1-(4-Methanesulphonamidophenyl)-4-(4-methanesulphonamidophenethyl)-piperazine hydrochloride hemi-hydrate**

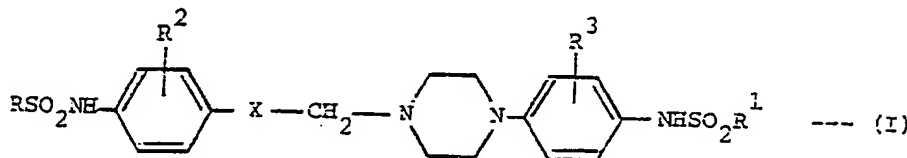
1-(4-Methanesulphonamidophenyl)-4-(4-methanesulphonamidophenethyl)piperazine [1.61 g. - see Example 1(C)] was dissolved in 2N aqueous hydrochloric acid (3.9 ml) and the reaction mixture was evaporated to dryness, giving a solid containing a trace of a reddish impurity. This solid was dissolved in methanol (250 ml) and boiled with charcoal (0.5 g), filtered, and the filtrate evaporated to about 65 ml, re-charcoaled (1.5 g. charcoal), and re-filtered. The filtrate was evaporated to about 20 ml, filtered, and ether (20 ml) was added. The solution was then evaporated to about 20 ml and more ether (10 ml) was added. The solution was left to cool, the resulting crystals were filtered off, washed with ether/methanol (40 ml 1:1 then 30 ml 2:1), then with ether (30 ml) and finally dried in vacuo. The yield of the pure title salt, m.p. (dec.) 254-6°, was 1.37 g.

Analysis %:-

Found: C,48.43; H,5.86; N,11.09;
 Calculated for $C_{20}H_{22}N_4O_4S_2 \cdot HCl \cdot \frac{1}{2}H_2O$: C,48.22; H,6.07; N,11.25.

Claims

1. A compound of the formula:-



or a pharmaceutically acceptable salt thereof,

wherein R and R¹, which are the same or different, are C₁-C₄ alkyl, C₃-C₇ cycloalkyl, -CH₂CF₃, -CH₂Cl, -CF₃ or -NH₂;

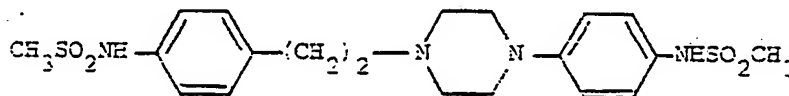
R² and R³, which are the same or different, are H, halo, CF₃, C₁-C₄ alkyl or C₁-C₄ alkoxy;

and X is -CH₂-, $\begin{array}{c} \text{C} \\ || \\ \text{O} \end{array}$ -

or -CH(OH)-.

2. A compound as claimed in claim 1 wherein R and R¹ are each CH₃; R² is H; and R³ is H, CH₃, Cl or F.

3. A compound as claimed in claim 1 which has the formula:-

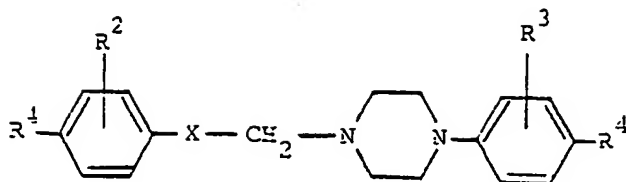


4. A pharmaceutical composition comprising a compound of the formula (I) as claimed in any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier.

5. A compound of the formula (I) as claimed in any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, for use as a medicament.

6. The use of a compound of the formula (I) as claimed in any one of claims 1 to 3, or of a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use in the prevention of reduction of cardiac arrhythmias.

7. A compound of the formula:-

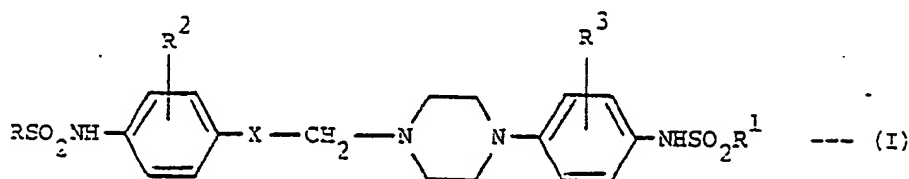


where X, R² and R³ are as defined in claim 1 and each R⁴, which is the same, is -NO₂ or -NH₂.

8. A compound as claimed in claim 7 wherein R² and R³ are H and X is -CH₂.

Claims for the contracting States: AT and ES

1. A process for preparing a compound of the formula:-



or a pharmaceutically acceptable salt thereof.

wherein R and R¹, which are the same or different, are C₁-C₄ alkyl, C₂-C₇ cycloalkyl, -CH₂CF₃, -CH₂Cl, -CF₃ or -NH₂;

R² and R³, which are the same or different, are H, halo, CF₃, C₁-C₄ alkyl or C₁-C₄ alkoxy;

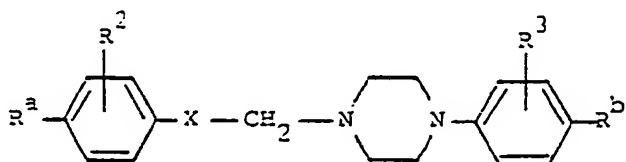
and X is -CH₂, -C-

||
O

or -CH(OH)-;

characterised by either:-

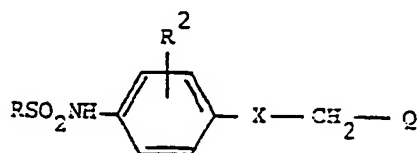
(a) reacting a compound of the formula:-



where X, R² and R³ are as defined for formula (I) and R^a and R^b, which are the same or different, are -NH₂ or -NHSO₂R where R is as defined for formula (I), with the proviso that at least one of R^a and R^b is -NH₂,

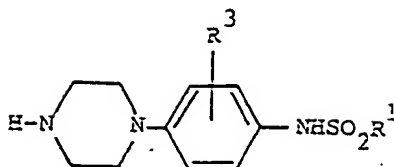
with sulphamide, a compound of the formula R¹SO₂Y where R¹ is as defined for formula (I) and Y is Cl or Br, or a compound of the formula (R¹SO₂)₂O where R¹ is as defined for formula (I) except for -NH₂; or

(b) reacting a compound of the formula:-



where X, R and R² are as defined for formula (I) and Q is a leaving group,

with a compound of the formula:-



where R^1 and R^3 are as defined for formula (I);

said process (a) or (b) being followed by, optionally, either or both of the following steps:-

(i) reduction of a compound of the formula (I) in which X is -CO- to a compound in which X is -CH(OH)- or -CH₂-; and

(ii) conversion of a compound of the formula (I) into a pharmaceutically acceptable salt.

2. A process according to claim 1(a), characterised in that the reaction is carried out in the presence of a base.

3. A process according to claim 1(b), characterised in that the leaving group is halo, C₁-C₄ alkanesulphonyloxy, benzenesulphonyloxy or p-toluenesulphonyloxy, and in that the reaction is carried out in the presence of a base.

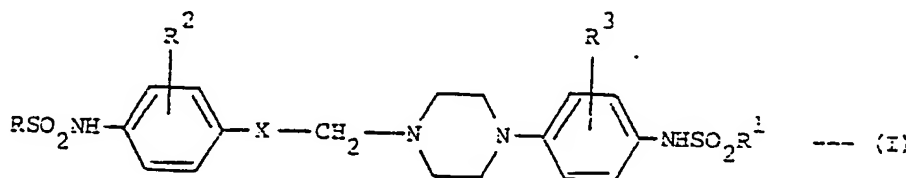
4. A process according to claim 2, characterised in that 1-(4-methanesulphonamidophenyl)-4-(4-methanesulphonamidophenethyl)piperazine is prepared by acylating 1-(4-aminophenyl)-4-(4-aminophenethyl)piperazine with methanesulphonyl chloride or methanesulphonic anhydride in the presence of a base.

5. A process according to claim 4, characterised in that the acylation is carried out using methanesulphonyl chloride in pyridine.

6. A process for preparing a pharmaceutical composition, characterised by mixing a compound of the formula (I) as defined in claim 1, or a pharmaceutically acceptable salt thereof, with a pharmaceutically acceptable diluent or carrier.

Claims For The Following Contracting State: GR:

1. A process for preparing a compound of the formula:-



or a pharmaceutically acceptable salt thereof,

wherein R and R^1 , which are the same or different, are C₁-C₄ alkyl, C₃-C₇ cycloalkyl, -CH₂CF₃, -CH₂Cl, -CF₃ or -NH₂;

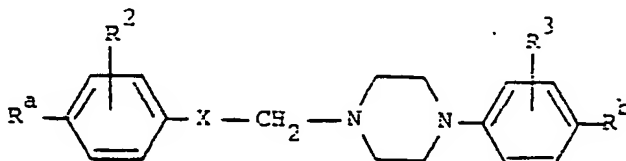
R^2 and R^3 , which are the same or different, are H, halo, CF₃, C₁-C₄ alkyl or C₁-C₄ alkoxy;

and X is -CH₂-, -C(=O)-

or -CH(OH)-;

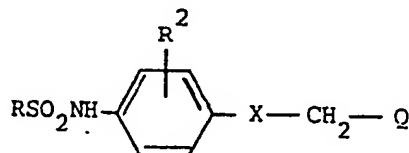
characterised by either:-

(a) reacting a compound of the formula:-

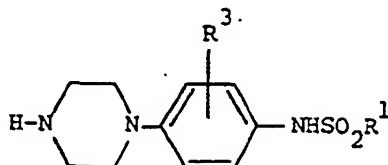


where X, R^2 and R^3 are as defined for formula (I) and R^a and R^b , which are the same or different, are -NH₂

or $\text{-NHSO}_2\text{R}$ where R is as defined for formula (I), with the proviso that at least one of R^a and R^b is -NH_2 , with sulphamide, a compound of the formula $\text{R}'\text{SO}_2\text{Y}$ where R' is as defined for formula (I) and Y is Cl or Br, or a compound of the formula $(\text{R}'\text{SO}_2)_2\text{O}$ where R' is as defined for formula (I) except for -NH_2 ; or
 (b) reacting a compound of the formula:-



where X, R and R^2 are as defined for formula (I) and Q is a leaving group, with a compound of the formula:-



where R^1 and R^3 are as defined for formula (I);

said process (a) or (b) being followed by, optionally, either or both of the following steps:-

- (i) reduction of a compound of the formula (I) in which X is -CO- to a compound in which X is -CH(OH)- or $\text{-CH}_2\text{-}$; and
- (ii) conversion of a compound of the formula (I) into a pharmaceutically acceptable salt.

2. A process according to claim 1(a), characterised in that the reaction is carried out in the presence of a base.

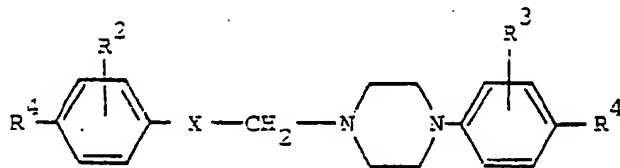
3. A process according to claim 1(b), characterised in that the leaving group is halo, $\text{C}_1\text{-C}_4$ alkanesulphonyloxy, benzenesulphonyloxy or p-toluenesulphonyloxy, and in that the reaction is carried out in the presence of a base.

4. A process according to claim 2, characterised in that 1-(4-methanesulphonamidophenyl)-4-(4-methanesulphonamidophenethyl)piperazine is prepared by acylating 1-(4-aminophenyl)-4-(4-aminophenethyl)piperazine with methanesulphonyl chloride or methanesulphonic anhydride in the presence of a base.

5. A process according to claim 4, characterised in that the acylation is carried out using methanesulphonyl chloride in pyridine.

6. A process for preparing a pharmaceutical composition, characterised by mixing a compound of the formula (I) as defined in claim 1, or a pharmaceutically acceptable salt thereof, with a pharmaceutically acceptable diluent or carrier.

7. A compound of the formula:-



where X, R^2 and R^3 are as defined in claim 1 and each R^4 , which is the same, is -NO_2 or -NH_2 .

8. A compound as claimed in claim 7 wherein R^2 and R^3 are H and X is $\text{-CH}_2\text{-}$.



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

EP 87 30 6922

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. CL.4)
A	LU-A- 42 041 (MAY & BAKER LTD) * Pages 2-7; example 18 *		C 07 D 295/12 A 61 K 31/495
A	DE-A-1 964 423 (F. HOFFMANN-LA ROCHE) * Pages 1-3, 5-8, 21 *		
			TECHNICAL FIELDS SEARCHED (Int. CL.4)
			C 07 D 295/00 A 61 K 31/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 18-11-1987	Examiner PAUWELS G.R.A.
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

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